REMARKS

I. Introduction

This communication is submitted in response to the Office Action dated July 13, 2004. No amendments to the application are requested at this time. Claims 17-35 and 37-44 remain in the application. Reconsideration of the application is requested.

II. Examiner Interview Summary

Record is made of a brief personal interview October 15, 2004, between Applicants' attorney, Karen Canady, and Examiner Katcheves, in connection with the present patent application. During this interview, discussion centered on reconsideration of the evidence previously submitted in support of enablement. General agreement was reached that the evidence already of record should suffice to overcome the enablement rejection. To clarify reasons for allowance, Applicants discuss the evidence below.

III. Non-Art Rejections

At pages 2-6 of the Office Action, the rejection of claims 17-35 and 37-44 under 35 U.S.C. §112, first paragraph, was maintained. The rejection was based on reasons of record and an alleged lack of enabling disclosure provided by the specification. Applicants respectfully traverse this rejection and maintain that the extensive evidence already of record establishes that the application as originally filed teaches one skilled in the art how to make and use the claimed invention. Although extensive data have been presented in previous responses, all of which contribute to supporting enablement of the claimed invention, Applicants highlight below select portions of these data showing the successes achieved with small fragment homologous replacement (SFHR) of the invention.

A. Fragment replacement and functional correction occur *in vivo*.

The Declaration Under 37 C.F.R. §1.132 by Dieter C. Gruenert ("Gruenert Declaration") submitted with the Amendment filed on September 26, 2003, provides data demonstrating functional correction of ion transport properties to normal ranges in the nasal mucosa in SFHR-treated mice in an *in vivo* model of cystic fibrosis (CF). These studies indicate that delivery of a wild-type

mCFTR fragment into the nasal mucosa of ΔF508 CF mice will change the cAMP-dependent ion transport properties of the mice, in that they now secrete Cl^- in response to cAMP stimulation. The Office Action dated July 13, 2004, provides no reasoning why these data fail to support enablement of the claimed invention. Applicants maintain that these data provide ample evidence that the claimed method of SFHR is enabled by the teachings of the specification.

B. Fragment replacement and functional correction occur *ex vivo*.

The Goncz et al. manuscript submitted as Exhibit B on September 26, 2003, demonstrated subsequent expression of the replacement fragment in human hematopoietic stem/progenitor cells (HSPC) following SFHR-mediated modification of β-globin sequences. The Goncz et al. abstract submitted as Exhibit G with the Amendment filed on December 3, 2001, demonstrates successful engraftment of SFHR-modified cells in mice, showing both efficient and stable conversion of β-globin in HSPC. In addition, the publication by Kapsa et al., submitted as Exhibit F with the Amendment filed on December 3, 2001, demonstrates successful *ex vivo* correction of the dystrophin gene in an animal model of muscular dystrophy, and reports that the *ex vivo* corrected cells survive after being injected back into muscle *in vivo*.

The data presented in these various exhibits show that the claimed method works: that an exogenous DNA fragment with flanking noncoding homologous sequence adjacent to the 3' and 5' ends of at least one replacement exon can be used successfully to replace a target fragment of a gene in a cell, be that cell *in vivo* or *ex vivo*. The data further show that the replacement results in functional correction and that cells having undergone this replacement *ex vivo* survive upon placement back into the body.

The Examiner, at page 3 of the Office Action, dismisses the data presented in the Prokophysin et al. paper submitted as Exhibit A on September 26, 2003, which paper provides additional evidence that cells undergoing SFHR *ex vivo* can be successfully engrafted into the body. The Examiner dismissed these data because the mouse models used in Prokophysin et al. are immune compromised and, therefore, allegedly fail to address potential problems with the host immune system. The Examiner notes that another factor in the efficacy of gene therapy methods is the immune system of the host organism. The Examiner is inappropriately assuming that problems encountered in other

types of gene therapy, wherein one or more foreign gene(s) are introduced into the host, are applicable to Applicants' invention. Applicants respectfully note, however, that the claimed invention is advantageous because the use of small fragment homologous replacement means that it does not require the use of vectors and foreign genes. The Examiner has not given sufficient basis for disregarding the successful data presented in Prokophysin et al. and the other Exhibits. The Examiner is also reminded that the *in vivo* data provided in the Gruenert Declaration does not involve the use of immune deficient mice. Accordingly, the demonstration of enabling support for the claimed invention cannot be disregarded because of a hypothetical problem that is not supported by the data.

The Examiner is respectfully reminded that the claimed method to be enabled is directed at replacing a target fragment of a gene in a cell. This method has been amply demonstrated to work. The claim does not require 100% efficiency or complete cure of a disease state. It simply requires replacing a target fragment of a gene in a cell, and this method is all that needs to be enabled. The Patent Office has provided no basis to question the ability of one skilled in the art to replace a target fragment of a gene using the teachings of the specification.

C. Fragment replacement works with a variety of delivery methods.

The various Examples and Exhibits demonstrate successful SFHR using both microinjection and lipid-based delivery systems. The *in vivo* data described in the Gruenert Declaration was derived using lipofectamine DNA complexes. Applicants note that the Examiner, at page 5 of the Office Action, stated that the Goncz et al. paper of Exhibit C did not serve to show the specification was enabling because none of the delivery vehicles used in Exhibit C were taught or suggested in the specification. This statement is in error. Both Exhibit C and the Gruenert Declaration used lipofectamine as a delivery vehicle. Lipofectamine as a delivery vehicle is explicitly taught in the specification at page 42, line 11 (discussing the data presented in Figure 13). In addition, lipid-based delivery systems are taught throughout the specification (at pages 24-25, at page 73, line 12, and at page 75, line 32, to page 76, line 14).

In addition to lipid-based delivery, successful replacement has been achieved using mechanical delivery systems (microinjection, electroporation). These strategies are described in the specification (e.g., at page 23, lines 25-30; and at page 25, lines 1-17). The variety of suitable delivery approaches is discussed in the specification at page 24, lines 25-29, and at page 40, as well as throughout the Examples

portion. Accordingly, the teachings of the specification do in fact describe the delivery methods used in the Exhibits and in the Gruenert Declaration.

Applicants have provided extensive evidence to demonstrate that the specification teaches how to practice the claimed method, both *in vivo* and *ex vivo*, and using multiple methods of delivery and in various disease models. Applicants respectfully request the rejections based on the alleged lack of enabling disclosure be withdrawn.

IV. Withdrawn Rejections & Terminal Disclaimer

At page 2 of the Office Action, the previous rejections of claims 17-35 and 37-44 based on the prior art were withdrawn. The previous rejection under the doctrine of obviousness double patenting was maintained, and Applicants' intent to file a terminal disclaimer upon indication of allowable subject matter was noted.

V. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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